JAK Inhibitors and Monoclonal Antibodies for the Treatment of Atopic Dermatitis: Final Policy Recommendations

August 17, 2021

Policy Recommendations

Following its deliberation on the evidence, the Comparative Effectiveness Public Advisory Council engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on the use of oral abrocitinib, baricitinib, and upadacitinib, topical ruxolitinib cream, and subcutaneous tralokinumab. The policy roundtable members included three patient advocates, two clinical experts, two payers, and three representatives from the drug maker(s). The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants.

A recording of the conversation can be accessed here, and a recording of the voting portion of the meeting can be accessed here. More information on Policy Roundtable participants, including conflict of interest disclosures, can be found in the appendix of this document. ICER's report on these treatments, which includes the same policy recommendations, can be found here.

All Stakeholders

All stakeholders have a responsibility and an important role to play in ensuring that effective new treatment options for patients with atopic dermatitis are introduced in a way that will help reduce health inequities.

Safe and effective treatment for atopic dermatitis, especially for those with moderate to severe disease, remains a significant unmet health care need. Efforts are needed to ensure that new therapies for atopic dermatitis such as oral abrocitinib, baricitinib, and upadacitinib, topical ruxolitinib cream, and subcutaneous tralokinumab, improve the health of patients and families and do not aggravate existing health inequities. Clinical experts and patients highlighted that the high cost of new therapies may worsen disparities in accessing care. This may be due to lack of health insurance that limits access to specialists and the new therapies that they prescribe, or high deductible payments even for those with insurance may result in steep out of pocket costs. The cost of care is not the only factor that may contribute to health inequities. Our clinical experts noted that the appearance of the skin is a key contributor to measures of disease severity, and individuals with darker skin types may be assessed as having less severe skin involvement. Since educational materials often include photos of individuals with atopic dermatitis who have lighter skin types, those with darker skin may be more likely to be misdiagnosed.

To address these concerns:

Manufacturers should take the following actions:

- Follow the precedent of responsible pricing set by Sanofi/Regeneron with dupilumab and set the price for new treatments for atopic dermatitis in fair alignment with added benefits for patients.

- Take steps necessary to include a more diverse patient population in clinical trials, including adequate number of patients with ethnic and racial backgrounds who have darker skin types.

Payers should take the following actions:

- Ensure that benefit designs developed in conjunction with employers and other plan sponsors do not create requirements for out-of-pocket spending that create major barriers to appropriate access for vulnerable patients

Clinical specialty societies should take the following actions:

- Develop and disseminate educational materials and create measurable goals to demonstrate that clinicians are aware of the challenges of diagnosing atopic dermatitis in patients with darker skin types.

Payers

The large number of patients with varying levels of severity of atopic dermatitis, combined with the potential for side effects and the high annual prices for newer generation treatments, will lead payers to develop prior authorization criteria and to consider other limits on utilization.

Perspectives on specific elements of cost sharing and coverage criteria for oral abrocitinib, baricitinib, and upadacitinib, topical ruxolitinib cream, and subcutaneous tralokinumab within insurance coverage policy are discussed below.

Coverage Criteria

- **Age:** Age criteria are likely to follow the FDA label for each drug and will not be expanded to cover earlier ages in the case of drugs not approved for adolescents or children. Similarly, although there may be greater uncertainty in outcomes for younger patients, it seems unlikely that payers will use clinical trial eligibility criteria to narrow coverage if the FDA approval includes treatment of adolescents. Payers should have efficient mechanisms for clinicians to seek coverage exceptions for patients with serious unmet need who are near the cutoff for the age necessary for coverage.

- **Clinical eligibility**: There is no clear consensus on how to operationalize a definition of the FDA indication for treatment of patients with "moderate to severe" atopic dermatitis. The severity of atopic dermatitis can vary substantially over time and, from a patient's perspective, can include a complex combination of intensity of itch, location, body surface area involvement, and degree of skin impairment. Some payers will allow clinician attestation, whereas others will adopt criteria based on clinical trial eligibility. Given the variability of patient phenotype and lack of familiarity among clinicians with scoring systems used in clinical trials, it is advisable for payers to create a broad, clinically relevant definition inclusive of multiple specific measures of disease intensity, e.g. "any of the following: BSA ≥ 10%, IGA ≥ 3, EASI ≥ 16," or "affected BSA ≥ 10% OR involvement of body sites that are difficult to treat with prolonged topical corticosteroid therapy (e.g. hands, feet, face, neck, scalp, genitals/groin, skin folds) or severe itch that has been unresponsive to topical therapies."

- In addition to a definition of severity, payers are likely to require that patients have received an adequate trial of topical therapy, e.g., a 30-day trial of prescription topical corticosteroid and/or topical calcineurin inhibitor OR the use of these medications is not medically advisable (as occurs with eyelid involvement). Payers should not require that this trial of topical agent(s) be immediately prior to the requested prescription; medical records indicating prior trial of topical therapy be sufficient.

- Potential criteria requiring prior use of phototherapy or systemic off-label treatment with agents like methotrexate is covered in the section on step therapy below.

- Ruxolitinib cream, if approved by the FDA, will likely have an indication for treatment of "mild to moderate" atopic dermatitis. The clinical criteria for coverage may be based on clinical trial eligibility (BSA ≥ 3% excluding scalp OR IGA 2-3) but will also likely require prior use of topical corticosteroids or calcineurin inhibitors. Another indication could be allowing the use of ruxolitinib cream in patients with severe atopic dermatitis for areas that do not clear adequately with systemic therapies.

- **Exclusion criteria**: There are no special medical comorbidities at this time that would serve as exclusion criteria for these treatments.

- **Duration of coverage and renewal criteria**: Initial coverage will likely be for a period of six to 12 months, which is long enough for dose titration, assessment of side effects, or disease progression.

- Clinical experts and payers felt that it would be appropriate to require attestation for continuation of therapy. The timing of such renewal may depend to some extent upon the specific therapy. For example, oral JAK inhibitors appear to have a quicker onset of action

than biologics such as dupilumab or tralokinumab. Patients and clinicians felt that requiring submission of outcome measures to support continuation was not needed. For biologics that are given by injection, patients reported that they would not want to continue use in the absence of improvement. For JAK inhibitors, given the potential for uncommon but serious side effects, long-term use in the absence of considerable benefit may also be unlikely. Most clinical experts suggested a three- to six-month period prior to renewal to be appropriate.

- **Provider restrictions**: Clinical experts agreed that it is reasonable to restrict prescriptions for dupilumab, abrocitinib, baricitinib, tralokinumab and upadacitinib to dermatologists or allergy specialists. Some payers may consider allowing prescription by generalist physicians able to work in consultation with specialists. The new therapies for moderate to severe atopic dermatitis require knowledge about evaluating and treating patients that most primary care clinicians are unlikely to have. Specialty clinicians are better suited to identify patients who are most likely to benefit, provide sufficient information for patients to make a well-informed decision, and monitor for response and side effects. Ruxolitinib cream may be covered with less restrictions on prescriber qualifications, but because it may be used in younger patients some payers may still wish to limit prescribing, at least initially, to specialists or generalist clinicians working in consultation with specialists.

Step Therapy

Payers should only use step therapy when it provides adequate flexibility to meet the needs of diverse patients and when implementation can meet high standards of transparency and efficiency.

Clinical experts and patient representatives stated that delayed and restricted access to treatment due to step therapy requirements for patients with moderate to severe atopic dermatitis is common. While it is possible to tailor step therapy in a clinically responsible fashion, it is often administered with documentation burdens and inadequate procedures for exceptions that make step therapy a source of great frustration and the cause of poor outcomes for some patients due to the discontinuation of medicine/missed doses. A particular area of concern raised by patients involved requirements to re-step through previously failed therapies when insurance changed.

Payers establishing step therapy with less expensive, off-label systemic agents and/or phototherapy should allow patients and clinicians to choose from multiple options rather than require patients to try multiple options.

Currently available specialty society guidelines are out of date and updated versions are expected in the coming year that may help shape policies regarding appropriate step therapy. Clinical experts

at the ICER meeting stated that it may be reasonable for payers to require patients to step through a less expensive off-label systemic therapy, but these therapies have well-known adverse effects and limited efficacy data that make it clinically inappropriate to require patients to attempt trials with all options prior to obtaining coverage for one of the newer agents. Prior agents include cyclosporine, azathioprine, methotrexate, mycophenolate mofetil, and interferon gamma. Cyclosporine may be a reasonable first-line agent for some patients, but the risk of renal toxicity requires patients to switch to another treatment after 6-12 months, so patients should not be required to try this agent after having an inadequate response to another systemic agent such as methotrexate that may be used for longer term use.

It is reasonable to include phototherapy as an option for first-step therapy, but lack of availability in many locations makes it inappropriate for payers to require patients to try phototherapy before receiving coverage for other options. The only exception would be a health plan/system that can provide good access to phototherapy at an out-of-pocket expense comparable to medication treatment options.

If multiple agents for severe atopic dermatitis are approved, payers should make available at least one biologic (dupilumab and/or tralokinumab) and at least one oral JAK inhibitor given how different these classes are in their onset of action and their risk profile. Clinician experts emphasized that the heterogeneity of atopic dermatitis and the challenges in defining and measuring disease severity support the need for having access to a range of different therapies. Specifically, clinical experts did not feel it would be appropriate to use step therapy that makes only one treatment available as the first step agent across biologics and oral JAK inhibitors. Some patients only have severe disease on a seasonal basis, making continual biologic treatment potentially less desirable than periodic use of a JAK inhibitor. Similarly, patients with asthma or more year-round severity are better candidates for biologic treatment. Clinical experts therefore strongly urged that at least one agent from both classes be available within any step therapy policy.

For ruxolitinib cream use in patients with mild to moderate atopic dermatitis, policy round table participants felt that stepping through other topical therapies such as a corticosteroid or calcineurin inhibitor was reasonable. Some clinical experts felt that since ruxolitinib cream may be used for younger patients as a steroid sparing medication, requiring stepping through a more potent topical steroid may not be appropriate. Manufacturers, Payers and Patient Advocacy Groups

Support pricing and rebate reform efforts that will create better rewards for clinical and economic value while also helping patients access and afford the treatments they need

It is widely recognized that the high prices of new prescription medications limit access to patients who may benefit from their use. Current pricing for medications is complex and the practice of using rebates and other methods to obscure the price of a therapy makes it difficult to assess whether the price being paid is in line with its effectiveness. Manufacturers and payers during the

policy round table highlighted the potential impact of value-based pricing as helping to promote transparency, affordability and promote access to new therapies. For example, upadacitinib has a much higher price after estimated rebates than other treatments, and it is possible that this drug can compete with a higher price largely because its manufacturer can tie formulary placement to rebates provided by other drugs made by that same manufacturer. This phenomenon, commonly known as "rebate walls," may in some cases provide an overall lower net cost to the payer, but it may only drive up the bubble between the list price and the net price for the benefit of pharmacy benefit managers and/or wholesalers, and it also creates true barriers to competition for new agents that have fewer indications or which are not made by companies that have other products whose rebates can be bundled together in negotiation. Unfortunately, there are no easy solutions to the role of rebates in the current system, but policy round table participants agreed that the federal government, plan sponsors, and other policy makers should work together to try to develop new approaches, such as indication-specific pricing, that can be piloted to create a pathway toward an end to the dominant role of bundled rebates.

Specialty Societies

Update treatment guidelines for patients with atopic dermatitis to reflect current treatment options in a form that is easy to interpret and use by clinicians, patients, and payers

Clinical societies should update their practice guidelines for managing patients with mild to moderate and moderate to severe atopic dermatitis to include newer therapies such as abrocitinib, baricitinib, dupilumab, tralokinumab and upadacitinib. Payers base their coverage decisions and integration of utilization tools to a great extent on clinical guidelines. The American Academy of Dermatology last updated it guidelines for the treatment of atopic dermatitis in 2014. The Joint Task Force on Practice Parameters for Allergy and Immunology, comprised of the American Academy of Allergy, Asthma, and Immunology, the American College of Allergy, Asthma, and Immunology, and the Joint Council of Allergy, Asthma, and Immunology issued updated treatment guidelines for atopic dermatitis in 2012. Current guidelines do not include newer approved agents for patients with atopic dermatitis such as dupilumab, approved by the FDA in 2017 or crisaborole cream, approved by the FDA in 2016; guidelines also do not discuss newer therapies that have not yet received FDA approval, such as IL-13 receptor antagonists and JAK inhibitors.

Policy round table participants highlighted that guidelines should not only provide information on options to be used by clinicians and patients for shared decision making, but also offer pragmatic advice about how to select specific therapies for specific subgroups. Payers expressed the need for updated guidelines from clinical societies with detailed guidance to permit meaningful stepped therapy approaches that permit reasonable clinical exceptions. For example, guidelines should distinguish use of agents in adolescents versus adults where there may be differences in the willingness to accept small but potentially serious risks and the need for rapid onset of improvement.

Manufacturers and Researchers

Establish long-term registries that can be used to assess the benefits and harms of chronic use of oral JAK inhibitors for patients with atopic dermatitis

Concerns about uncommon but potentially serious risks of oral JAK inhibitors such as serious infections, cancer, blood clots and cardiovascular events when used for other conditions have led to boxed warnings. Whether these harms will also be seen when used in patients with moderate to severe atopic dermatitis requires larger, long-term follow-up studies that assess not only the durability of response but these infrequent risks among individuals using oral JAK inhibitors versus other biologic therapies such as dupilumab. Even the topical JAK inhibitor, ruxolitinib cream, has topical absorption and may warrant long-term follow-up, especially since it may be used in younger individuals. Even if it is not associated with systemic toxicity, topical ruxolitinib cream use might increase the risk of skin cancers.

Conduct research that directly compares real-world treatment options and sequential treatment effectiveness

Multiple stakeholders expressed concerns about the lack of information directly comparing new treatments and the need for active comparator trials. With the potential for having multiple newer therapeutic options that work through different mechanisms for patients with mild to moderate and moderate to severe atopic dermatitis, there is a great need for pragmatic research trials that compare different medications as they will be used by patients and clinicians in real world settings. Appropriate head-to-head trials would inform decision making by patients and clinicians. Trials that compare multiple treatment options, sequences and combinations are needed to identify comparative effectiveness, durability of benefit, and adverse effects. For example, trials should compare the net benefits of different oral JAK inhibitors or the tolerability and acceptance of oral versus injectable therapies for patients with moderate to severe disease.

Support the development of improved measures of disease severity and outcomes that are meaningful to patients

Clinical experts identified the lack of standard definitions of disease severity in atopic dermatitis as a challenge to identifying homogeneous patient populations for inclusion in clinical trials. We also heard from patient advocacy groups that endpoints used in clinical trials do not always measure what is most important to patients and families. For example, many endpoint measures focus on the appearance of the skin, something that may be important for an adolescent or young adult, but may be less important for older patients. Though there are measures of itch, sleep, and interference in quality of life, these outcomes are not yet combined in ways that reflect the heterogeneity needed. Moreover, they are rarely translated into utility measures that can be incorporated into cost effectiveness analyses. Patient groups can take a leading role in collecting

real-world data, as well as collaborating with researchers, manufacturers, and regulators to define a core set of severity and outcome measures and then in promoting their use in all clinical trials.

Appendix

Appendix Tables 1 through 3 contain conflict of interest (COI) disclosures for all participants at the July 23, 2021, Public meeting of the New England CEPAC.

Appendix Table 1. ICER Staff and Consultants and COI Disclosures

ICER Staff and Consultants	
Foluso Agboola, MBBS, MPH, Vice President of Research, ICER*	**Serina Herron-Smith**, BA, Senior Research Assistant, Evidence Synthesis, ICER*
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*No conflicts of interest to disclose, defined as individual health care stock ownership (including anyone in the member's household) in any company with a product under study, including comparators, at the meeting in excess of $10,000 during the previous year, or any health care consultancy income from the manufacturer of the product or comparators being evaluated.

Appendix Table 2.New England CEPAC Panel Member Participants and COI Disclosures

Participating Members of CEPAC	
Robert Aseltine, PhD, Professor and Chair, Division of Behavioral Sciences and Community Health, UCONN Health*	**Greg Low**, RPh, PhD, Director, MGPA Pharmacy Quality and Utilization Program, Massachusetts General Hospital*
Austin Frakt, PhD, Director, Partnered Evidence-Based Policy Resource Center, VA Boston Healthcare System*	**Eleftherios Mylonakis,** MD, PhD, FIDSA, Professor of Infectious Disease, Chief of Infectious Disease, Brown University*
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Stephen Kogut, PhD, MBA, RPh, Professor, University of Rhode Island College of Pharmacy*	**Jason L. Schwartz,** PhD, Associate Professor of Health Policy, Yale School of Public Health*
Donald M. Kreis, MS, JD, Consumer Advocate, New Hampshire Office of the Consumer Advocate*	**Jason Wasfy**, MD, MPhil, Medical Director, Mass General Physician's Organization[ŧ]
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*No conflicts of interest to disclose, defined as individual health care stock ownership (including anyone in the member's household) in any company with a product under study, including comparators, at the meeting in excess of $10,000 during the previous year, or any health care consultancy income from the manufacturer of the product or comparators being evaluated.

[ŧ]Dr. Wasfy did not participate as a voting member of the New England CEPAC during this meeting.

Appendix Table 3. Policy Roundtable Participants and COI Disclosures

Policy Roundtable Participant	Conflict of Interest
Samantha Bittner, Patient Ambassador, National Eczema Association	No financial conflicts to disclose.
Thomas Brownlie, MS, Senior Director, Pfizer Inc.	Thomas is a full-time employee of Pfizer Inc.
Jeffrey Casberg, MS, RPh, Vice President of Pharmacy, IPD Analytics	Jeffrey is a full-time employee of IPD Analytics.
Michele Guadalupe, MPH, Associate Director of Advocacy and Access, National Eczema Association	The National Eczema Association has received grants and sponsorship awards from a variety of industry partners, including Pfizer, AbbVie, Sanofi, Regeneron, Incyte, and LEO Pharma.
Catherine Herren, PharmD, MS, Advisor, Value Development, Eli Lilly, and Company	Dr. Catherine Herren is a full-time employee of Eli Lilly and Company.
Kyle Hvidsten, MPH, Vice President, Head of Global Health Economics and Value Assessment, Sanofi	Kyle is a full-time employee of Sanofi.
Erik Schindler, PharmD, Director, Emerging Therapeutics and Outcome-Based Contracting, UnitedHealthcare Pharmacy	Dr. Erik Schindler is a full-time employee of UnitedHealthcare Pharmacy.
Elaine Siegfried, MD, Professor of Pediatrics and Dermatology, Saint Louis University School of Medicine	Dr. Elaine Siegfried has received consulting fees and honoraria from industry partners, including Incyte, Regeneron, Sanofi, LEO Pharma, Pfizer, and AbbVie for participation in clinical trials as a PI. She also received funding from Pfizer to support a two-year fellowship position at Saint Louis University.
Jonathan Silverberg, MD, PhD, MPH, Associate Professor, George Washington University School of Medicine and Health Sciences	Dr. Jonathan Silverberg has received funding from industry partners, including AbbVie, Eli Lilly, Incyte, LEO Pharma, Regeneron, and Sanofi.